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The Prognostic Significance of Different Definitions for Angiosome-Targeted Lower Limb Revascularization

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Background: The definition of angiosome-targeted revascularization is confusing, especially when a tissue lesion affects several angiosomes. Two different definitions of direct revascularization exist in the literature. The study aim was (1) to compare the 2 definitions of direct revascularization in patients with foot lesions involving more than one angiosome and (2) to evaluate which definition better predicts clinical outcome.

Methods: This study cohort comprises 658 patients with Rutherford 5–6 foot lesions who underwent infrapopliteal endovascular or surgical revascularization between January 2010 and July 2013. We compared the 2 angiosome-targeted definitions using multivariate analysis; the impact of each angiosome-targeted definition was adjusted for a propensity score obtained by means of nonparsimonious logistic regression.

Results: Direct revascularization according to definition A was performed in 367 cases (55.8%) versus 198 cases (30.1%) with definition B. The propensity-score-adjusted analysis showed that definition A of direct revascularization was associated with significantly better wound healing ($P < 0.044$, hazard ratio [HR] 1.291) and lower amputation rates ($P < 0.047$, HR 0.706), whereas definition B was associated only with significantly better wound healing ($P < 0.029$, HR 1.321). The prognostic ability of direct revascularization according to definition A was confirmed in a Cox proportional hazard analysis.

Conclusions: Definition A of direct revascularization was associated with a significantly higher wound healing and leg salvage rate than indirect revascularization in both series. Therefore, it seems that, if the wound spreads over several angiosomes in the forefoot or heel, any angiosome involved in the wound can be targeted.

INTRODUCTION

Recently, the angiosome concept has offered a new perspective on revascularization in patients with critical limb ischemia (CLI) and tissue loss. An

angiosome was defined by Taylor and Palmer¹ as a three-dimensional block of tissue supplied and drained by specific, “angiosomal vessels.”

Attinger et al.² presented that the foot consist of 6 angiosome regions, each supplied by one of the crural arteries and its terminal branches. The concept of angiosome-targeted (direct) revascularization is based on this division. Direct revascularization (DR) refers to the selective revascularization of the specific artery feeding the angiosome that is affected by an ulcer. If angiosome-targeted revascularization is successful, direct flow from the abdominal aorta to the angiosomal vessel is achieved.^{3,4}

Two meta-analyses, including a total of 15 studies, have reported that wound healing and limb salvage, especially in patients with diabetes, are better after DR.^{5,6} However, the definition of

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DR is not clear and, in many of the studies, the definition is lacking altogether. Most of the studies accept an approach as DR if the angiosome with the affected surface is revascularized, with the exception of the forefoot and heel where any angiosome involved in the wound can be targeted.^{3,4,7–11} This exception, however, does not apply to a new definition suggested by Alexandrescu¹² in his book, *Angiosomes Application in Critical Limb Ischemia in Search for Relevance*. DR for wounds located in the forefoot and heel is defined as a procedure on the posterior tibial artery only. Furthermore, the definition of the angiosome-guided approach in cases where the wound spans several angiosome regions is scarce.

As recently reported, the wound is located across more than one angiosome in the majority of patients with CLI and tissue lesions.¹³ There is a high predominance of tissue loss located in the toes, metatarsal heads, and the heel.¹⁴ Therefore, we aimed to investigate which of the 2 existing definitions of DRs predicts better wound healing and leg salvage.

MATERIALS AND METHODS

The study plan was accepted by the Ethical Committee of the Helsinki University Central Hospital.

Patients

This retrospective study included 774 consecutive patients with CLI and tissue loss (Rutherford 5–6), who underwent infrapopliteal endovascular or surgical revascularization in our institution between January 2010 and June 2013. Only patients with a foot lesion spreading over several angiosomes or located in more than one angiosome were included. Exclusion criteria were previous infrainguinal revascularization and incomplete information on the status of the foot.

Definitions

An ischemic foot ulcer was defined as a full-thickness skin defect distal to the malleolar level presented for at least 2 weeks with a toe pressure of <50 mm Hg. If toe pressure could not be obtained for some reason (pain, noncompressible artery, or necrosis), the transcutaneous partial pressure of oxygen was measured, with a level of <30 mm Hg indicating an ischemic lesion.

The revascularization techniques in our institution have been described earlier.^{3,15} Our policy is to perform percutaneous transluminal angioplasty (PTA) as a first-line revascularization in stenotic

lesions, short occlusions, and in patients who have increased risk for bypass surgery or no autologous vein available. In case of long occlusions in patients who are fit for surgery and do have autologous vein, the policy is to do bypass first. Before PTA, all patients were taking aspirin (100 mg/day). All patients continued life-long aspirin therapy accompanied with clopidogrel for 3 months (75 mg/day) after the procedure. Patients treated by endovascular approach first had isolated infrapopliteal lesion in 343 (78.5%) cases; no stent was used for these crural lesions. For bypass surgery, the single-segment great saphenous vein graft (nonreversed, placed under fascia) was used in 64.3%, spliced vein grafts in 30.3%, composite vein with prosthesis in 4.1%, and prosthetic graft in 1.4%. Intraoperative heparin was administered before graft insertion. The patients received low-molecular-weight heparin (1 mg/kg/day) during their hospital stay accompanied with life-long aspirin therapy (100 mg/day) unless contraindicated.

In the literature, 2 definitions of DR in the case of a foot ulcer spreading over the forefoot and heel are available. Definition A accepts DR if any of the affected angiosomes are revascularized^{3,7–11}; for example, if the lesion is located in the tip of the toes or the toes are amputated due to gangrene, procedures on either the anterior tibial artery/pedal artery or the posterior tibial artery/plantar arteries, or both, are considered angiosome-targeted. While definition B only accepts the revascularization of posterior tibial artery/plantar arteries as an angiosome-targeted procedure¹² (Table I).

In cases of a foot ulcer spreading over several angiosomes in other location than the forefoot or heel, we adopted the same approach as described in the study by Iida et al.^{16,17} DR was defined as a procedure on the artery supplying the largest surface of the angiosome involved in the lesion. For example, large necrotic lesion in the dorsum foot of spreading to the medial foot instep, or lesion located at the level of lateral malleolus continuing to dorsum of the foot. In such case, arteria tibialis anterior ± arteria dorsalis pedis would be the corresponding artery for revascularization.

If the patient suffered from multiple foot ulcers located in separate angiosomes, all affected angiosomes had to be revascularized for the intervention to count as DR.

Wound Location

We adopted the general scheme of angiosomal distribution³ to evaluate the number of affected angiosomes. Ever since we started the research on angiosome concept in 2009, ischemic tissue defect

Table I. Scheme showing which artery needs to be revascularized in cases where the wound spreads over several angiosomes in the location of the forefoot or heel

Revascularization	Definition A		Definition B	
	Direct	Indirect	Direct	Indirect
Forefoot	ATA/ADP ± ATP/plantar arteries	AF	ATP/plantar arteries	ATA, AF
Heel	AF ± ATP/plantar arteries	ATP/ADP	ATP/plantar arteries	ATA, AF

ADP, arteria dorsalis pedis; AF, arteria fibularis; ATA, arteria tibialis anterior; ATP, arteria tibialis posterior.

and its location have been carefully described in the patient's records. Therefore, the location and severity of the tissue loss was obtained by reviewing our clinical notes by 2 observers, a trainee of vascular surgery with anatomical background and a vascular surgeon with clinical experience more than 15 years. In 95 cases, photographs were available and compared with clinical notes. In many cases, the tissue defect was severe (gangrene, infection) and required periprocedural digit amputation or metatarsal amputation. In such cases, the wound was immediately affecting 2 or 3 angiosomes, depending on the amputation level.

Wound Healing and Follow-up

The wound care depended on the characteristics of each lesion: debridement of necrotic tissue, surgical revision of infected ulcers together with microbial therapy, and the application of a skin graft in cases where primary or secondary closure was not possible.³ A healed wound was defined as complete epithelialization of the tissue defect by secondary intent or after any additional local ulcer surgery. The wound was considered nonhealed if it was still open at the end of the follow-up.

After revascularization, patients remained under routine surveillance in the outpatient clinic by a vascular nurse who carried out a duplex ultrasound examination of the revascularized artery and followed the foot status; a vascular surgeon was consulted if necessary. In the case of PTA, the visits were scheduled at 1, 3, and 6 months after revascularization, and in the case of a bypass graft at 1, 3, 6, and 12 months after revascularization. If the duplex examination of bypass graft showed signs of stenosis, the patient underwent control digital subtraction angiogram (DSA) within 2 weeks; a PTA to bypass graft was performed in case of confirmed stenosis. If the wound opened after routine duplex surveillance ended, the patient continued visits to the outpatient clinic until the wound healed. The follow-up ended and the wound was considered as nonhealed if the patient underwent a new infringuinal bypass due to failure of primary intervention

(endovascular or surgical), new additional PTA of crural arteries after primary intervention, or a major amputation due to nonhealing foot ulcer or occluded bypass graft, or if the patient died.

Data Collection

Data collection was performed using our prospectively collected database and scrutinizing it retrospectively by reviewing patient records as well as the patient's imaging files. In patients who underwent endovascular treatment, DSAs before and after revascularization were reviewed to evaluate whether an angiosome-targeted procedure had been performed, and in patients undergoing surgical bypass, the preoperative magnetic resonance angiograms and DSAs, if available, were reviewed as well. All patients treated by PTA had on-table DSA right after revascularization as a control of possible complications (dissection, microembolism).

The patient's baseline characteristics and operative data are summarized in [Table II](#).

Estimated glomerular filtration rate (eGFR) was estimated by the Modification of Diet in Renal Disease formula (Levey).

Outcome Measures

We compared the outcome of DR versus indirect revascularization (IR) using the 2 above-described definitions. The primary outcome measures were wound healing and leg salvage. Survival was a secondary outcome end point.

Statistical Analysis

Statistical analysis was performed using SPSS version 22.0 statistical software (IBM SPSS, Inc., Chicago, IL). No attempt to replace missing values was made. Fisher's exact test, the chi-squared test, and the Mann–Whitney and Kaplan–Meier tests were used for univariable analysis. Multivariate analysis for assessing the impact of baseline variables on late outcome was performed using the Cox proportional hazards method. The impact of each DR definition was adjusted for a propensity

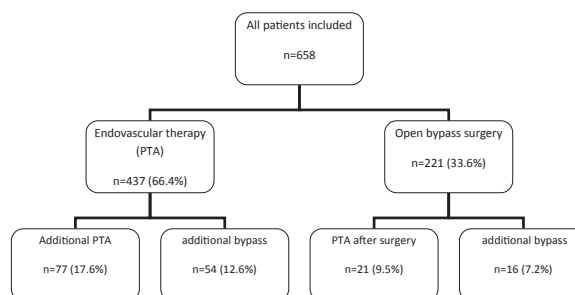
Table II. Baseline characteristics of patients undergoing lower limb revascularization according to 2 different definitions of direct (angiosome-targeted) revascularization

Variable	Definition A			Definition B		
	Indirect 291 patients	Direct 367 patients	<i>P</i> value	Indirect 460 patients	Direct 198 patients	<i>P</i> value
Age	75.5 ± 11.3	73.8 ± 11.1	0.047	75.6 ± 11.0	72.1 ± 11.5	<0.0001
Female	107 (36.8)	139 (37.9)	0.771	181 (39.3)	65 (32.8)	0.113
Smoking habit	41 (14.1)	55 (15.0)	0.746	61 (13.3)	35 (17.7)	0.141
Pulmonary disease	38 (13.1)	37 (10.1)	0.233	58 (12.6)	17 (8.6)	0.136
Atrial fibrillation	94 (32.3)	99 (27.0)	0.136	147 (32.0)	46 (23.2)	0.024
Hypertension	195 (67.0)	220 (59.9)	0.062	293 (63.7)	122 (61.6)	0.612
Estimated glomerular filtration rate	74.9 ± 36.1	76.3 ± 39.2	0.663	74.8 ± 36.4	77.9 ± 41.0	0.360
Dialysis	11 (3.8)	29 (7.9)	0.028	22 (4.8)	18 (9.2)	0.048
Kidney transplantation	4 (1.4)	6 (1.6)	0.786	4 (0.9)	6 (3.0)	0.074
Diabetes	176 (60.5)	233 (63.5)	0.430	280 (60.9)	129 (65.2)	0.299
Coronary artery disease	118 (40.5)	127 (34.6)	0.117	180 (39.1)	65 (32.8)	0.125
Heart failure	39 (13.4)	45 (12.3)	0.663	60 (13.0)	24 (12.1)	0.745
Stroke	44 (15.1)	48 (13.1)	0.453	65 (14.1)	27 (13.6)	0.867
C-reactive protein (mg/dL)	46.3 ± 53.8	47.9 ± 54.2	0.835	49.5 ± 54.4	41.7 ± 52.5	0.004
C-reactive protein >10 mg/dL	197 (67.7)	254 (69.2)	0.678	330 (71.7)	121 (61.1)	0.007
Gangrene	69 (23.7)	124 (33.8)	0.005	138 (30.0)	55 (27.8)	0.566
No. of affected angiosomes	2.3 ± 1.1	2.2 ± 0.7	0.815	2.3 ± 0.9	2.0 ± 0.8	<0.0001
Complete pedal arch	45 (15.5)	87 (23.7)	0.009	79 (17.2)	53 (26.8)	0.005
Bypass surgery	88 (30.2)	133 (36.2)	0.106	143 (31.1)	78 (39.4)	0.039

score obtained by nonparsimonious logistic regression including all variables listed in Table I. Separate propensity scores were estimated for each definition. The regression models were calibrated by the Hosmer–Lemeshow Goodness-of-Fit Test. Model discrimination was evaluated using the area under the receiver operating characteristic (ROC) curve. All tests were two-sided with the alpha level set at 0.05 for statistical significance.

RESULTS

After the exclusion criteria, the cohort resulted in a total of 658 patients, of which 437 (66.4%) were treated by PTA and 221 (33.6%) by infrapopliteal surgical bypass. Of 658 patients, 367 (55.8%) fulfilled the criteria for direct lower limb revascularization when definition A was used. When definition B was applied, the number of cases who underwent DR was significantly smaller, 198 (30.1%, $P < 0.05$). The baseline and operative characteristics in patients with DR compared with those with IR according to both definitions are summarized in Table II. The mean follow-up was 21 months (standard deviation 13.8 months, range 0–51). In the endovascular group, 29.9% of patients underwent reintervention compared with 16.7% in bypass surgery (Fig. 1). Two hundred three (30.9%) patients

**Fig. 1.** Reintervention rates according to revascularization method.

underwent minor amputation (130 toe and 73 metatarsal amputations) during the follow-up. It is worth noting that DR according to definition A resulted in a rather balanced distribution of baseline characteristics. When examining definition A of DR, the patients were significantly younger and a higher proportion of them had a complete pedal arch visible at angiography, but they also had a significantly higher prevalence of dialysis and foot gangrene than patients who underwent IR (Table II). In contrast, patients who underwent DR according to definition B were also significantly younger and had a lower prevalence of atrial fibrillation, a lower number of affected angiosomes, a higher prevalence of a complete pedal arch at angiography,

Table III. Propensity-score-adjusted outcome according to 2 different definitions of direct revascularization

Outcome end points	Definition A		Definition B	
	<i>P</i> value	HR (95% CI)	<i>P</i> value	HR (95% CI)
Wound healing	0.044	1.291 (1.007–1.656)	0.029	1.321 (1.029–1.695)
Major amputation	0.047	0.706 (0.501–0.996)	0.096	0.697 (0.456–1.066)
Mortality	0.938	0.990 (0.761–1.286)	0.087	0.764 (0.561–1.040)

Table IV. Outcome end points adjusted for diabetes, estimated glomerular filtration rate, C-reactive protein, revascularization method, number of affected angiosomes, and presence of intact pedal arch according to 2 different definitions of direct revascularization

Outcome end points	Definition A		Definition B	
	<i>P</i> value	HR (95% CI)	<i>P</i> value	HR (95% CI)
Wound healing	0.037	1.294 (1.016–1.648)	0.060	1.267 (0.990–1.621)
Major amputation	0.044	0.703 (0.847–0.990)	0.045	0.652 (0.429–0.990)
Mortality	0.356	0.886 (0.685–1.146)	0.043	0.733 (0.543–0.991)

and lower baseline levels of C-reactive protein; however, they had a higher prevalence of dialysis than their counterparts who underwent IR.

Unadjusted actuarial analysis showed that, irrespective of the definition (A or B) that was used, DR yielded better wound healing and leg salvage rates when compared with IR: if definition A was applied, the wound healing rates in the DR versus IR groups at 1 year were 72.3% vs. 66.6% (log-rank: $P = 0.031$), respectively, and the leg salvage rates at 1 year were 83.4% vs. 75.6% ($P = 0.019$), respectively. If definition B was applied, the respective wound healing rates at 1 year were 74.9% vs. 67.3% (log-rank: $P = 0.019$) and the respective leg salvage rates at 1 year were 87.4% vs. 76.8% ($P = 0.003$).

A logistic regression model including all variables listed in [Table II](#) provided a propensity score for definition A of DR (Hosmer–Lemeshow test: $P = 0.183$) with an area under the ROC curve of 0.635 (95% confidence interval [CI] 0.593–0.677) and for definition B a propensity score (Hosmer–Lemeshow test: $P = 0.659$) with an area under the ROC curve of 0.686 (95% CI 0.643–0.729).

A propensity-score-adjusted analysis showed that, when definition A was adopted, DR was associated with significantly better wound healing and leg salvage rates, whereas when definition B was applied, DR was associated only with significantly better wound healing ([Table III](#)).

The prognostic ability of definition A was confirmed in a Cox proportional hazard analysis

as adjusted for diabetes, eGFR, C-reactive protein, revascularization method, number of affected angiosomes, and the presence of an intact pedal arch ([Table IV](#)). This model also showed a significant predictive value of DR according to definition B for leg salvage and mortality, but only a trend toward better wound healing. When both DR definitions were included in the latter regression model, only definition A was associated with better wound healing ($P = 0.040$, hazard ratio [HR] 1.286, 95% CI 1.012–1.635) and a lower risk of major amputation ($P = 0.038$, HR 0.698, 95% CI 0.497–0.980).

DISCUSSION

Even though 2 recent meta-analyses^{4,5} show a tendency toward better clinical outcome after angiosome-guided revascularization, many clinicians argue against the concept. In our recent study, we demonstrated that, in only 24% of the patients with CLI and tissue loss, the wound is limited to one angiosome and that, in the majority of cases, 2 or more angiosomes are affected.¹³ Furthermore, we have shown that the number of affected angiosomes is associated with wound healing time and inversely associated with wound healing rate.⁶

The majority of the studies does not report the number of affected angiosomes nor define the DR in cases where the wound affects several angiosomes.^{3,8–11,18–20} The study by Iida et al.^{16,17} targeted

the largest surface affected; due to the dual blood supply of the heel and digits, however, it is difficult to correctly define the DR of this regions.

In this study, we included an extensive series of patients who had lesions affecting more than one angiosome and in whom 2 different definitions of angiosome-targeted revascularization, as described in the methodology, were tested.

Although both definitions were associated with better wound healing, definition A also seemed to predict leg salvage when the risk factors were adjusted with propensity score analysis. Furthermore, the use of definition B was less successful clinically as it resulted in fewer cases in which DR was performed, 30% vs. 56% when definition A was used. This significant difference may be explained by the poorer feasibility of an angiosome-targeted procedure using definition B, as the clinician is limited to the posterior tibial artery as the only option for DR in cases where the wound is located in the forefoot or heel. Furthermore, we experience that the arteria tibialis posterior was in many cases severely diseased with long occlusions or multiple (pearl-like) lesions, therefore the easier artery was chosen for endovascular treatment.

It is worth noting that the patients in the targeted revascularization group were divided in terms of their characteristics when definition A was compared with definition B. Patients for whom DR was achieved according to definition B had fewer comorbidities and less severe foot lesions as graded by the number of affected angiosomes, in addition to having lower baseline levels of C-reactive protein when compared with the patients treated with DR according to definition A.

While the study by Higashimori et al.²¹ demonstrates that an existing intact pedal arch is essential when only one vessel runoff can be established to the foot, another study by Rashid et al.²² also suggests that the quality of the pedal arch is more important with regard to wound healing time than whether or not angiosome-guided revascularization is achieved. In this study, we evaluated the intactness of the pedal arch and found that patients with DR more often had an open pedal arch. However, this factor was adjusted with propensity score analysis and should not have an impact on the results.

To confirm the finding of the propensity score analysis, a Cox proportional hazards model was utilized. This multivariate analysis confirmed the finding with regard to definition A. In the Cox model, definition B also predicted leg salvage, but yielded only a trend toward better wound healing. The Cox model supports the superiority of definition A with regard to the angiosome concept.

Based on our findings, it seems that, if the wound spreads over more than one angiosome in the location of the forefoot or heel, any angiosomal artery involved in the wound can be targeted to achieve a better clinical outcome. Therefore, the clinician has more options to choose from, with a higher probability that revascularization will be possible in one of the arteries.

This is a retrospective study, and its main limitation is the description of wound location, which is extracted from case records. Even though wound location has been carefully reported in our institution ever since the emergence of interest in angiosomes and wound location in the literature, determination of the affected angiosome can be difficult in some cases. Furthermore, the study by Varela et al.⁴ showed the importance of collaterals in wound healing; they concluded that IR via collateral with good diameter can provide similar result as DR. This cohort, however, does not provide the information of collateralization and therefore it is a limitation to our study as it could influence our results.

Furthermore, in cases where graft occluded shortly after bypass surgery ($n = 15$) the wound was considered nonhealed in follow-up as reprocedure or major amputation was performed. Unsuccessful wound healing, however, was related to surgical failure rather than angiosome-guided revascularization.

The research on angiosome concept lacks a well-planned prospective study in which the wound location and size are defined precisely and where high-quality angiograms with information on collaterals as well as the patency of the pedal arch are performed and the wound healing is followed carefully. This kind of study would yield definitive information on the true influence of angiosome-targeted revascularization on leg salvage. The evidence so far, although based almost solely on retrospective reports and therefore not definitive, should guide interventionists toward the direction of angiosome-targeted revascularization when CLI patients with tissue lesions are treated.

CONCLUSION

Consensus needs to be achieved regarding the accurate definition of DR, especially if more than one angiosome is clinically involved. In this series, the proportion of patients meeting the criteria of DR using definition A was larger than when definition B was used. Definition A of DR was associated with a significantly higher wound healing and leg salvage rate than IR, and its prognostic significance was

not inferior to definition B. Based on our findings, it seems that, if the wound spreads over more than one angiosome in the location of the forefoot or heel, any angiosome involved in the wound can be targeted to achieve a better clinical outcome.

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